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November 24, 1998

Dr. Larry G. Hart
National Toxicology Program
Board Executive Secretary
111 Alexander Drive
P. O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Hart:

Philip Morris U.S.A. takes this opportunity to provide additional scientific commentary to the National Toxicology Program on its intent to review environmental tobacco smoke (ETS) for possible listing in the *Report on Carcinogens, Ninth Edition,* as noticed in 63 *Fed. Reg.* 5565, February 3, 1998 and 63 *Fed. Reg.* 57132, October 26, 1998. We have enclosed copies of the slides that will be used in our presentation at the December 2 and 3 meeting, and a review of the published results from the IARC multi-center study of exposure to ETS and lung cancer in Europe (Boffetta, P., Agudo, A., Ahrens, W., et al., *Journal of the National Cancer Institute*, 90 (19): 1440 - 1450, 1998). We are sending these materials by fax and overnight mail.

Please let me know if I can provide any further information.

Sincerely,

Richard A. Carchman, Ph.D.
Vice President
Research, Development & Engineering

Analysis of "Multicenter Case-Control Study of Exposure to Environmental Tobacco Smoke and Lung Cancer in Europe,"
Boffetta, P., Agudo, A., Ahrens, W., et al.,
Journal of the National Cancer Institute
90 (19): 1440-1450, 1998

A. Introduction

The long-awaited publication of the IARC multicenter epidemiological study, designed to investigate the possible association of reported environmental tobacco smoke (ETS) exposure with lung cancer, has been recently published in the *Journal of the National Cancer Institute*. This study is not only one of the largest case-control epidemiological studies which has been carried out to investigate this possible association, but also one of the best conducted. The results of this study suggest an extremely weak, not statistically significant numerical association between reported spousal or workplace ETS exposure and lung cancer (OR = 1.16, 95%; CI, 0.93-1.44 and OR = 1.17; 95% CI, 0.94-1.45, respectively). The authors report no associations between reported ETS exposure in social situations or during childhood and lung cancer in non-smokers.

This analysis will begin with a summary of the study, followed by a brief discussion of the reported results. Following this will be a detailed analysis of the results in order to determine if, as suggested by an accompanying editorial (Blot, W. J., and McLaughlin, J. K., 1998), "...the inescapable scientific conclusion is that ETS is a low-level lung carcinogen." This analysis will address two factors; namely, the possible contribution of systematic biases to the reported odds ratios, and the general ability to draw conclusions regarding associations between ETS exposure and lung cancer based on the existing published epidemiological data.

B. Description of the Study

1. Study Design

The study was a multicenter, case-control study with 12 centers from Europe contributing. To a large extent each center used the same design; however, there were some differences noted among the centers. The most important differences are summarized below. They are addressed in detail in the body of our analysis.

a. Selection of controls

Control subjects were hospital based in the centers from France, Portugal, Spain, and one of the Italian centers (Italy 3). Control subjects were both hospital and community based (percentages not given) in the center from the UK. All other control subjects were community based. It should be noted that all hospital controls with smoking related diseases were excluded from the control groups in all centers. In addition, there was an inconsistency among centers with respect to the matching of cases and controls. Individual matching was done for some centers but others used frequency matching.

b. Diagnostic criteria for case eligibility

The report states that "in selected centers, case subjects without a histologic or a cytologic diagnosis were also included." There is no information given as to the number of centers which included cases without histologic or cytologic confirmation of diagnosis, nor is there any information as to the overall percentages of such cases without this confirmation. On the other hand, the report points out that 96.5% of the cases had microscopically confirmed disease.

c. Inclusion of smokers

Smokers were studied in all but the Portuguese centers. The term "smokers" in this case refers to individuals who smoked not more than 400 cigarettes lifetime.

According to the publication, the study was designed to have a power of 80% to detect a relative risk of 1.3 significant at the 95% confidence level.

2. Subjects

The study included 650 non-smoker lung cancer cases where non-smoker, as indicated above was defined as having smoked less than 400 cigarettes in a lifetime. As was also noted above, lung cancer was confirmed by either cytology or histology for 96.5% of all cases. A total of 1542 control subjects took part in the study. Response rate, particularly for controls, appeared to vary quite substantially among the centers. It was less than 50% for two of the German centers and one of the Portuguese centers. These three centers contributed more than 30% of the total cases. With respect to the remaining centers, the publication simply states that the response rates were 55% to more than 95%. Clearly these low response rates for at least 3 of the centers could have produced significant bias in the results, but there is no way to evaluate the possible extent of such bias.

The distribution of cases among the study centers is uneven. Most notable is the major contribution made by the three German centers, greater than 35% of the total cases, whereas all other countries contributed only around 10%.

3. Measurement of ETS exposure

A common questionnaire was used to estimate ETS exposures. Methodology for estimating amounts of exposure differed according to what exposure metric was being examined.

a. Childhood exposure

Quantitative variables used in the estimation of childhood ETS exposure (exposures up to age 18) included the number of smokers in the household and the cumulative exposure. The latter was expressed as the number of years of exposure weighted for the type of smoker – mother, weight of 1; father, weight of 0.75; and other adults, weight of 0.25. These weights were reportedly based on urinary cotinine concentrations in children.

b. Spousal exposure

Quantitative variables for estimating exposure to ETS from the spouse within marriage, as well as from other cohabitants, included the following: 1) the total number of years of exposure; 2) the product of the number of years and the number of hours per day of exposure; 3) the average number of cigarettes smoked per day by the spouse in the presence of the index subject; and 4) the cumulative exposure expressed as pack-years and derived from the product of variables 1 and 3 listed above. For reported exposure to ETS from sources other than cigarettes the following conversion factors were used. The number of cigarillos smoked was multiplied by 2, and for cigars and pipes, the number was multiplied by 3. The authors state that a relatively small percentage of ETS exposure came from sources other than cigarettes, and exclusion of these data would not have in any way changed the results.

c. Workplace Exposure

Quantitative variables for reported workplace ETS exposure were the total number of years of exposure and the total number of years of exposure weighted for the number of hours of exposure per day and for a "subjective index of smokiness in the workplace." No information was provided as to how the "subjective index of smokiness in the workplace" referred to above was obtained.

Data were also collected relating to time since either reported spousal or workplace exposure ceased.

For each source of reported exposure, investigation of possible dose-response trends was carried out as follows. Cases and controls who reported no exposure to ETS were considered as the reference group. Exposed individuals were grouped into three categories defined as below the 75th percentile, between the 75th and 90th percentile or above the 90th percentile. Two-tailed tests for linear trends were carried out by testing the significance of the regression parameter of a trend variable which also included the reference category.

4. Other factors considered

The common questionnaire apparently also collected information on demographic variables, residential history (including cooking and heating arrangements), and exposure to known or suspected occupational lung carcinogens. Eight of the centers also collected some data on dietary intake from which were derived indicators of intake of vegetables, fruits, β-carotene, total carotenoids, and retinol. Potential confounders that were analyzed by the regression analysis were educational level (as a variable with three categories based on center-specific cut points), proportion of life spent in urban areas, occupational exposure to lung carcinogens, and intake of vegetables, β-carotene, total carotenoids, and retinol.

C. Results

1. Childhood exposure

Based on 389 cases and 1021 control subject reporting exposure during childhood, an overall odds ratio of 0.78 (95% CI, 0.64-0.96) was reported. The authors claim that there was a

significant decreasing trend as a function of increasing exposure with a test for trend of p = 0.02 (1.00, 0.83, 0.68, 0.90 with increasing level of cumulative exposure). It should also be noted that these figures include all subjects exposed during childhood whether they were exposed later in life or not. The authors do report that analysis of the data excluding all individuals reporting adult exposure gave results that were "similar... although more unstable because of the small numbers."

2. Spousal Exposure:

The study reports OR's for spousal exposure using two different indexes. The index chosen by the authors as being most representative of actual exposure is "self-reported exposure to spousal smoke." For this index the reported OR for all subjects was 1.16 (95% CI, 0.93-1.44) based on 344 case subjects and 700 control subjects. The other index used was "ever married to a smoker." The OR's reported for this index were 1.27 (95% CI, 1.00-1.62) for all subjects, 1.20 (95% CI, 0.92-1.55) for women, and 1.65 (95% CI, 0.85-3.18) for men. A summary of the results presented in the publication are displayed in the table below.

Subgroup analysis	OR (95% CI)	Comments
Overall population – "ever married to a smoker"	1.27 (1.00-1.62)	It would appear that "ever-married" also includes co-habitants that were not married.
Women	1.20 (0.92-1.55)	
Men	1.65 (0.85-3.18)	
"self-reported exposure to spousal smoke"	1.16 (0.93-1.44)	344 cases vs. 700 controls
Excluding "never married"	1.18 (0.92-1.51)	
Ever exposure to spousal smoke, stratified by sex Women Men	 1.11 (0.88-1.39) 1.47 (0.81-2.66)	 321 cases vs. 623 controls 23 cases vs. 68 controls
Duration (years of exposure) 0 1-34 35-42 ≥43	 1.00 1.05 (0.83-1.33) 0.63 (0.12-2.37) 1.07 (0.68-1.68)	P for trend = 0.10 305 cases vs. 838 controls 223 cases vs. 498 controls 65 cases vs. 103 controls 38 cases vs. 80 controls
Duration (hrs/day x yrs.) 0 1-135 136-223 ≥224	 1.00 0.90 (0.70-1.16) 1.20 (0.78-1.85) 1.80 (1.12-2.90)	P for trend = 0.02 297 cases vs. 778 controls 165 cases vs. 396 controls 44 cases vs. 81 controls 41 cases vs. 53 controls
Average exposure (cigs./day) 0 0.1-10 10.1-18.0 ≥18.1	 1.00 1.10 (0.86-1.40) 0.58 (0.35-0.90) 1.37 (0.85-2.20)	P for trend = 0.88 297 cases vs. 778 controls 206 cases vs. 411 controls 25 cases vs. 83 controls 35 cases vs. 55 controls
Cumulative exposure(pack yrs) 0 0.1-13.0 13.1-23.0 ≥23.1	 1.00 1.00 (0.78-1.28) 0.89 (0.57-1.39) 1.64 (1.04-2.59)	P for trend = 0.09 297 cases vs. 778 controls 188 cases vs. 411 controls 36 cases vs. 83 controls 42 cases vs. 55 controls
Adjusted for exposure to suspected or known occupational carcinogens	1.18 (0.94-1.46)	

Adj. for urban vs. rural residence	1.15 (0.91-1.45)	
Adj. for consumption of vegetables above or below median level	1.14 (0.89-1.45)	
Stratified by age <55y 55-64y 65-74y	 0.99 (0.64-1.52) 1.19 (0.80-1.76) 1.25 (0.89-1.75)	
Stratified by histology Small cell (11.3% of cases) Squamous cell (17.2% of cases) Adenocarcinoma(50.6% of cases)	 1.39 (0.79-2.45) 1.21 (0.77-1.91) 1.08 (0.82-1.42)	Not statistically significant. "For all major histologic types, a dose-response relationship was suggested with cumulative exposure and duration (in hours/day x years) of exposure to spousal smoke."
Exp. from cohabitant other than spouse Ever Exposed 0.1-13.0 pk yrs 13.1-25 pk yrs ≥25.1 pk yrs	 1.10 (0.88-1.36) 0.96 (0.74-1.23) 1.02 (0.66-1.59) 1.37 (0.85-2.20)	Based on only 44 cases unexposed to spousal smoke.

The authors claim that there is no significant heterogeneity of reported effect as shown by tests for heterogeneity (P = 0.42). They do note, however, that there is considerable inter-center variability with point estimates ranging from < 0.7 in one center to >1.5 in four centers.

The authors also claim that there is little effect of adjusting for the potential confounders that they included in their multiple regression analysis. As is often the case for such studies, however, they fail to address that they may have missed some potential confounders, that they may not be able to accurately measure confounding effects, or that the effect of all confounders combined could have had a greater effect on the relative risks.

3. Workplace exposure

The authors write: "A total of 374 case subjects and 855 control subjects reported ever exposure of ETS at the workplace, yielding an OR of 1.17 (95% CI, 0.94-1.45)." Results reported for workplace exposures are displayed in the table below.

Subgroup analysis	OR (95% CI)	Comments
Overall	1.17 (0.94-1.45)	374 cases vs. 855 controls
Women	1.19 (0.94-1.51)	269 cases vs. 476 controls
Men	1.13 (0.68-1.86)	105 cases vs. 379 controls
Duration (years) 0 1-29 30-38 ≥39	 1.00 1.15 (0.91-1.44) 1.26 (0.85-1.85) 1.19 (0.76-1.86)	P for trend = 0.21 276 cases vs. 687 controls 278 cases vs. 634 controls 55 cases vs. 129 controls 39 cases vs. 91 controls
Duration (level x hrs./day x yrs.) 0 0.1-46.1 46.2-88.9 ≥89.0	 1.00 0.97 (0.76-1.25) 1.41 (0.93-2.12) 2.07 (1.33-3.21)	P for trend <0.01 276 cases vs. 687 controls 196 cases vs. 525 controls 47 cases vs. 105 controls 48 cases vs. 71 controls
By histology Small cell Squamous cell Adenocarcinoma	 1.17 (0.67-2.04) 1.27 (0.82-1.97) 1.06 (0.81-1.40)	No statistical significant differences among types

The authors again note that there was no significant heterogeneity of reported effect among the centers. However, they do point out that eight of the centers reported OR's greater than 1.00, which presumably implies that four centers reported OR's equal to or less than 1.00.

Unlike reported spousal exposure, no pattern was reported for age at interview.

No data are provided for the effects of those potential confounders investigated. It was merely stated that educational level, occupational exposures, urban vs. rural living, and intake of vegetables/fruits, etc. had no appreciable effect on the OR's. It should be noted that the effect of educational level was not reported in the multiple logistic regression for the spousal data.

4. Combined spousal and workplace exposure

The OR for ever exposure either from the spouse or from the workplace was 1.14 (95% CI, 0.88-1.47). This result was based on a total of 527 case subjects and 1201 control subjects. All of the results are presented in the table below.

Subgroup analysis	OR (95% CI)	Comments
Ever exposure to either spousal or workplace ETS	1.14 (0.88-1.47)	527 cases vs. 1201 controls
Men	1.13 (0.68-1.89)	97 cases vs. 390 controls
Women	1.15 (0.86-1.55)	420 cases vs. 811 controls
Duration (in years)		P for trend = 0.13
0	1.00	115 cases vs. 331 controls
1-36	1.11 (0.85-1.46)	362 cases vs. 876 controls
37-43	1.26 (0.87-1.81)	82 cases vs. 185 controls
≥44	1.29 (0.87-1.92)	70 cases vs. 125 controls
Duration (hrs/day x years)		P for trend = 0.01
0	1.00	122 cases vs. 339 controls
0-165	0.91 (0.69-1.20)	289 cases vs. 749 controls
166-253	1.31 (0.88-1.94)	63 cases vs. 151 controls
≥254	1.46 (0.96-2.22)	57 cases vs. 101 controls
Time since exposure		
0	1.00	122 cases vs. 339 controls
≥16yrs	0.92 (0.67-1.26)	121 cases vs. 327 controls
3-15yrs	1.20 (0.89-1.62)	175 cases vs. 394 controls
0-2yrs	1.18 (0.88-1.59)	211 cases vs. 459 controls

As before, the authors claim that there was no significant heterogeneity of effect among centers (P = 0.82). However, there is considerable variability. Results ranged from a point estimate of 0.72 in France to 2.29 in Sweden. Three centers had point estimates of less than 1.00, while 9 centers had point estimates greater than 1.00.

The authors state that a "weak increase in lung cancer risk was present for increasing duration of exposure [in years]," and that the trend was stronger for duration measured in hours/ day x years. A dose-response was also claimed for duration of exposure with squamous cell and small cell carcinoma, but not adenocarcinoma, which represents ~50% of the cases included in this study.

5. Exposure in vehicles and public indoor settings

The results for variables representing reported exposure in vehicles and other public indoor settings are presented below.

Subgroup analysis	OR (95% CI)	Comments
Overall vehicles	1.14 (0.88-1.48)	125 cases vs. 310 controls
Overall public indoor settings	1.03 (0.82-1.29)	174 cases vs. 454 controls

The OR's for these reported exposures were not consistent among centers. For exposure in vehicles the point estimates ranged from 0 to 2.85, while for exposure in other public indoor settings, the range of the point estimates was 0.24 to 2.32. The authors stated that analysis by duration of exposure suggested no consistent pattern for these two sources of exposure.

D. Discussion

The results reported in the IARC study may be interpreted by some to suggest that there is a weak, numerical association between reported spousal and workplace ETS exposure and lung cancer. The question, however, is whether any reported association is likely to be meaningful, or is simply a result of a combination of various types of errors and systematic biases. Some of the potential systematic biases that could have resulted in an elevated relative risk are discussed in some detail within the publication. However, as will be seen below, IARC's treatment of these biases may not be adequate. In evaluating the meaning of the reported numerical association, the authors devote a large part of their discussion to a comparison of their results with results published in other studies. However, often such comparisons are inappropriate, since these differences can best be explained by either random variation or clear systematic biases. Several of these points will be discussed at length below.

1. Systematic Biases

a. Methodological Weaknesses

As with any epidemiological study, there are methodological weaknesses in the IARC study as well. However, the authors of this publication discuss potential methodological weaknesses quite frankly, and they have made an effort to estimate how such weaknesses have contributed to the reported results.

As was pointed out in the study design section above, some of the centers used hospital-based controls, whereas other centers selected community-based controls. The publication points out that there are possibilities for potential biases using either type of control. Hospital-based controls are more likely to suffer from selection bias; however, community-based controls are more likely to be subject to differential recall bias. Because of the fact that both methodologies were used, the authors compared results from subsets of centers defined according to their criteria for selection of control subjects. The OR for ever spousal or workplace exposure was 1.12 (95% CI, 0.75-1.66) for centers with hospital-based controls and 1.13 (95% CI, 0.80-1.61) for centers with community-based controls. The authors judge this difference to be small, and this review concurs with that judgment. However, the fact that there is agreement

between the two methods of control selection does not suggest that no bias was present, since each method is possibly subject to a different type of bias.

There were large differences in response rates among the centers, particularly with controls, with a number of centers having quite low response rates. Both the differences among study centers and the low response rate can result in selection bias. In order to determine if there may have been selection bias resulting from low response rates for some of the centers the authors carried out the following calculation. For each exposure index stated (childhood, workplace, and spousal) two regressions were performed – one of the log OR against non-response rates in cases, the other of the log OR against non-response rates in controls. Had non-response been a problem, it is likely that one would have seen a relationship between OR and non-response. However, no relationship was found suggesting that non-response was not a problem. Although simple, this analysis would initially seem a reasonable way of detecting major bias. However, non-response may be correlated with other features of the study, e.g., region, and such simple correlations may be misleading. A preferred method would have been to have included response rate in cases and controls in a multivariate analysis which looked at various features differing by center that may have affected the study-specific OR estimate.

Cytologic or histologic verification of lung cancer was not required as a criterion for inclusion of cases in the study. The authors restricted their analysis to histologically verified cases resulting in an OR for either spousal or workplace exposure of 1.11 (95% CI, 0.86-1.43). The difference between this OR and the OR for the total sample was also designated by the authors as being "minor." However, this correction represents a 21% decrease in excess risk. Such a difference cannot be regarded as minor. Moreover, the fact that the confidence interval was slightly more narrow than the confidence interval for the total sample suggests that the OR for those cases that lacked histological confirmation was both noticeably higher and contained much greater random fluctuation than the OR for the confirmed cases. Consequently, it would appear that restricting the analysis to those cases which were histologically confirmed would yield a better estimate of the true case population, and that an OR of 1.11 is a more reasonable estimate than is an OR of 1.14.

There was an inconsistency among study centers with regard to matching or not matching of controls. As a consequence, either all of the data could have been treated using unconditional multivariate regression, or conditional multivariate regression could have been used for centers with matched controls and unconditional multivariate regression for those centers without matched controls. Technically, the mixed conditional/unconditional methodology is regarded as being somewhat more accurate. IARC tested both methods, stating that "the results were similar for most of the variables analyzed (Fig. 1)." As a consequence of this similarity, only the unconditional OR's were reported. Again, as was the case for the difference between the OR's for cases with cytologic confirmation and all cases, what is described as minor differences are far from minor. The difference between the two procedures for reported spousal exposure is a decrease of only 0.01. However, the difference for either reported spousal or workplace exposure is 0.03, a decrease of 21% in excess risk, and the difference for reported workplace exposure is 0.07, a decrease of 41% in excess risk.

b. Misclassification of Smoking Status

The authors devote a considerable portion of their discussion to the issue of misclassification of smoking status, which they agree is "a potential source of bias in studies of lung cancer and ETS." Their conclusion is that misclassification has a very small effect on the OR's, and they propose three explanations to support this conclusion.

The first explanation was based on their analysis of the data with exclusion of those individuals whom they classified as occasional smokers. As noted above, the criterion with respect to smoking for inclusion in the study was smokers of less than 400 cigarettes lifetime. The authors make the assertion that misclassified smokers are more likely to be found in this group of acknowledged occasional smokers, and that when this group was excluded, there was no change in OR. The OR restricted to self-reported never smokers for spousal exposure was 1.15 (95% CI, 0.86-1.54) compared to 1.16 (95% CI, 0.93 - 1.44) when the entire data set was used. There is no question that these numbers are not substantially different. However, the assertion that misclassified smokers are more likely to be represented in self-reported occasional smokers (less than 400 cigarettes lifetime) than in self-reported never smokers is not adequately supported.

The authors' second explanation uses an assumption that rests on very slim evidence. The publication summarizes the conclusions reached by Lee and Forey (Lee, P. N., and Forey, B. A., 1996) stating that:

> If there is no true risk related to ETS exposure, a relative risk of the magnitude of that found in our study (i.e. 1.15) can be obtained assuming a misclassifcation rate of 2% (14), a proportion of smoking spouses of the order of 30-50%, a proportion of smokers in the underlying population of 20-40%, a concordance ratio of 3, and a relative risk of smoking in the order of 10-20.

The authors concede that all of these assumptions are reasonable with the exception of the last one. Instead they state that "[A] more reasonable relative risk of smoking of 2 [Nyberg, F. et al., 1997] would result in a relative risk due to misclassification of 1.01-1.02." A misclassification rate of 2% is clearly a reasonable assumption, since in an IARC supported study by Riboli, et al., (Riboli, E., et al., 1990, reference 14 in the first IARC citation above), a misclassification rate of 1.9% was reported for a sample of 1,369 non-smoking women. Riboli, et al., used a cut-off point of 100 ng cotinine/mg urinary creatinine to arrive at their misclassification rate of 1.9% (26 of the 1,369). If 1.9% of this sample had cotinine levels of at least this value, one can evaluate whether the relative risk of smoking of 2 used by Boffetta et al. is truly reasonable. Levels of cotinine in active smokers average about 1000 ng cotinine /mg creatinine. Therefore, each of the self-reported never-smokers who were true smokers as suggested by their cotinine levels had levels of at least 10% that of active smokers (Riboli, et al., do not give the actual level of cotinine found in these 26 subjects). It is extraordinarily unlikely that all of these subjects had levels of cotinine of exactly 100 ng cotinine/mg creatinine. If we make the very conservative estimate that the levels ranged from 100 to 500, with an average of 250 ng cotinine/mg creatinine, the estimated relative risk of lung cancer for the misclassified never smokers would be between 2.25 and 4. This

would result in a correction for misclassification of 0.03. This correction, which has to be regarded as highly conservative, would not appear to be very different from the correction suggested by the authors; however, once again, what appears to be a small correction generates a reduction of almost 20% in the excess risk attributed to spousal smoking.

The authors' justification for the value of 2 as the relative risk for misclassified never smokers can be found in a publication by Nyberg, et al. (Nyberg, F., et al., 1997, reference 24 in the second IARC citation above). Nyberg, et al., used a test and retest method for a Swedish twin cohort to identify misclassified smokers. They found a misclassification rate of 4.9% among men and 4.5% among women. They then calculated the relative risk for lung cancer for the group of misclassified smokers. This relative risk was 1.9 for men (there were 0 cases of lung cancer for women). However, this value of 1.9 was based on only two cases out of 285 subjects, and the 95% confidence limits were 0.4-9.1. Clearly, to determine a relative risk of 2 for misclassified never smokers based upon a single cohort study with such a small sample is hardly justifiable.

It is also important to point out that the authors' rejection of Lee and Forey's (1996) assumption of a relative risk of misclassified smokers of between 10 and 20 as being much too high seems to rest on a misinterpretation of the Lee and Forey publication. There is clearly a gradation of misclassified smokers ranging from occasional or former smokers all the way to current regular smokers. In order to attempt to use a single set of numbers, one can either take a weighted estimate of misclassified smokers, or a weighted estimated of relative risk. Lee and Forey assume a weighted estimate of misclassified smokers as being 2%, although their total estimate is considerably higher than that. Consequently, when the IARC publication assumes a misclassification rate of 2% and then also adjusts the relative risk downwards to 2, the correction for the fact that there is a range of misclassified smokers may have been made twice.

The IARC's publication's third explanation rests on a validation study that was carried out by Nyberg et al. (Nyberg, F., et al., 1998). This study, wherein next-of-kin were interviewed in order to confirm never-smoking status for 175 case subjects and 233 control subjects in the Swedish study group, found a misclassification rate of only 1.2%. However, the next-of-kin interview methodology is not particularly sensitive for the detection of misclassified smokers. The total sample of 408 individuals in Nyberg, et al., included 26 individuals who acknowledged that they were occasional or former smokers. Inspection of Table 2, page 175 of this publication, shows that 15 of these 26 individuals were classified by next-of-kin interviews as being never-smokers, that is smokers of less than 400 cigarettes lifetime. Therefore, a total of 57.7% of next-of-kin incorrectly classified self-reported former or occasional smokers as never-smokers. If next-of-kin interviews were so strikingly inaccurate in confirming self-reported smoking, it is not surprising that this technique would be too imprecise to detect more than a fraction of ever-smokers who did not acknowledge their smoking.

c. Confounders

The method used to treat confounders was unusual. Although information was collected on a number of potential confounding factors, data were presented for only

three of these confounders as potential modifiers for the OR for spousal ETS exposure; namely, exposure to suspected or known occupational lung carcinogens, urban, rural, or mixed urban and rural residence, and consumption of vegetables above or below the median. Moreover, instead of treating all possible confounders together in the multivariate analysis, adjusted OR's were presented for each possible confounding factor separately. In this analysis, the OR for spousal exposure was modified from 1.16 to 1.18 for occupational exposure, from 1.16 to 1.15 for urban or rural living, and from 1.16 to 1.14 for consumption of vegetables below the median. On the basis of these calculations, the authors claim that there is no effect due to confounding. Certainly, on the basis of these data, there is appears to be little effect. At best one can assume that the overall effect of the three confounders taken together would lower the spousal OR by only 0.01, only a 6% decrease in relative risk. However, it is unfortunate that the authors did not carry out a more thorough analysis. They claim that they "found no evidence that other known or suspected risk factors of lung cancer and their correlates, such as educational level used as a proxy for socioeconomic status, occupational exposure to carcinogens, residence in urban areas, and low consumption of vegetables explained the risks from ETS exposure either from the spouse or at the workplace." However, no data are presented that confirm this assertion.

This conclusion of the IARC study appears improbable, unless, of course, the authors mean by the above statement that such potential confounding factors cannot explain all of the reported increase in risk, which is probably accurate. First of all, their own data indicate a 12% decrease in excess risk when the OR for spousal exposure is adjusted for consumption of vegetables below the median. Secondly, there are a number of papers, which the authors cite, showing a clear correlation between marriage to a smoker and differences in other life style factors (Matanoski, G., et al., 1995; Thornton, A., et al., 1994; and Whichelow, M. J., et al., 1991). Nevertheless, lacking a more thorough analysis of the effect of potential confounding factors, it is not possible to suggest anything more than a minimal decrease in the OR as a result of such factors.

d. Overall Effect of Potential Biases

(1) Spousal Exposure

The OR cited by IARC for spousal exposure was 1.16 (95% CI, 0.93-1.44). Clearly, this result is not statistically significant, suggesting that it could have arisen by chance. On the other hand, when taken as a part of the totality of the evidence, it is not greatly different from OR's rising from other meta-analyses, and would certainly have only a minor effect on the pooled relative risk. The above analysis shows, however, that the value of 1.16 is an unadjusted value, and is certainly not the best value. The following adjustments need to be made: 1) 0.03 for smoking misclassification, 2) 0.03 for lack of cytologic confirmation of cases, 3) 0.01 for confounding, and 4) 0.01 for the use of only unconditional logistic regression. These very conservative adjustments reduce the OR to 1.08, a 50% decrease in excess risk.

(2) Workplace Exposure

The workplace OR cited by IARC was 1.17 (95% CI, 0.94 - 1.45). Again, this result, as was the result for spousal exposure, was not statistically significant. Once again, it has been claimed that this result is consistent with the overall results, and that therefore the lack of statistical significance is irrelevant. However, significant adjustments can be made to this result as well; namely, 1) 0.07 for the use of unconditional logistic regression as opposed to mixed conditional/ unconditional regression, 2) 0.03 for lack of cytologic confirmation of lung cancer, and 3) 0.03 for smoker misclassification. This results in a decrease of 0.13 giving an adjusted result for the OR for workplace exposure of 1.04.

(3) Either Workplace or Spousal Exposure

The corrections which need to be applied to this OR of 1.14 are: 1) 0.03 for smoker misclassification, 2) 0.03 for the use of only unconditional logistic regression, 3) 0.03 for lack of cytologic confirmation of lung cancer, and 4) 0.01 for confounding effects. These corrections result in a corrected OR of 1.04.

(4) Summary

Application of data taken directly from the IARC study publication demonstrates that adjustments to the OR's can be made which result in an OR for spousal exposure of 1.08, for workplace exposure of 1.04, and for spousal or workplace exposure of 1.04. Had IARC utilized these adjustments, it is unlikely that the resulting OR's would have been considered as demonstrating any real association. It should be mentioned that these corrections are quite conservative, and that not all factors that could have biased the results have been considered, such as differential recall bias and interviewer bias. Moreover, virtually all of the ETS lung cancer studies that have been published to date suffer from most, if not all of these biases, some of them to a much greater extent. Unlike the IARC study, however, most of them have not presented enough data to estimate the extent of the necessary adjustments.

The claim has often been made that there is not one single bias that can account for the numerically elevated risks in ETS/lung cancer studies. This is probably correct. However, when one totals the small corrections that each bias contributes, the reported increase in risk may no longer be evident.

2. Comparison of IARC Results with Other Epidemiological Studies

The Discussion section of the IARC publication devotes considerable space to a comparison of their results with other results. As will be seen below, the authors attempt to explain sometimes small differences in OR's between their study and other key studies by attributing these differences to real effects. However, a key question remains, does the precision of epidemiology allow one to assume that such comparisons are at all meaningful?

To at least initiate this answer it is worthwhile to examine the internal variability within IARC's data. As already pointed out there were sizable differences in the spousal or workplace OR's

exposure among study centers, with results ranging from an OR of 0.72 in France to 2.20 in Sweden. To put these differences in perspective had, by chance, the three groups with the highest ORs been excluded (Sweden, and Portugal 1 and 2), the calculated OR would have been about 1.03 (95% CI, 0.78-1.35), resulting in a conclusion of no increased risk at all. On the other hand, had the three groups with the lowest ORs been omitted (France, Germany 1 and Italy 1), the OR would have been a statistically significant 1.44 (95% CI, 1.05-1.96). It is easy to say that inclusion of all the data results in a more precise value, but by no means is one certain that such a value is at all accurate.

The differences are large even when one restricts oneself to the examination of multiple centers within the same country. The OR's for the three German centers for reported workplace or spousal exposure are 0.88, 1.22, and 2.01. As can be seen, one center has an OR less than 1.0, one has a slightly elevated OR, while the third has an OR that is greater than 2.0. This variability is even more striking when one considers that the same methodology was used for all three centers, and that the questionnaire was in a common language. The three Italian centers are less striking, with OR's of 0.73, 1.12, and 1.39, but even here the variability is apparent.

IARC clearly recognizes the inconsistency among study centers. As the authors point out, "[t]he lack of consistency of the results among the study centers may limit the strength of our findings and the conclusions we can derive from them." Nevertheless, they defend their overall result by pointing out that the differences among centers were, for the most part, not statistically significant. Does this mean that we should assume, for example, that ETS exposure is a true risk for Swedes but not for the French? Or should we assume that there were clear biases present in one center but not the other? The fact that IARC's own data are not consistent, strongly suggests that differences in epidemiological results are not necessarily reflective of a real difference in conditions or outcomes.

IARC proposes, for example, that the fact that their results were clearly lower than those from studies in Greece was a consequence of the fact that most subjects in the IARC study reported having ended their exposure several years before the interview, whereas the Greek studies were "conducted in a population in which most subjects classified as exposed to spousal ETS were currently exposed." The authors have claimed that there is no increased risk associated with exposure that ceased 15 years before the interview (OR = 0.92, 95% CI, 0.67-1.26). However, it is interesting to note that the OR for exposure which ceased 3-13 years before the interview was 1.20 (95% CI, 0.80-1.62), whereas the OR for those subjects who were currently exposed or who ceased exposure less than 3 years before the interview was 1.18 (95% CI, 0.88-1.59). Moreover, the number of cases in the group where reported exposure had ceased more than 15 years before the interview was only 121, whereas there were 386 cases in the two groups with more recent reported exposure. Therefore, the statement that most subjects had ended their ETS exposure before the interview, although correct, is not relevant, since most subjects were in groups which had an elevated OR despite the fact that they ended their exposure before the interview. Lastly, the differences among the three OR's are not statistically significant, and it is quite possible that if such a study were repeated, very different results would emerge. A much better explanation of the difference between these results and the Greek studies is that the IARC study was larger and conducted in such a way to minimize, although not completely eliminate, systematic biases.

The short discussion regarding the comparison of this publication's findings regarding reported childhood exposure and other studies is particularly illuminating. The authors point

out that Janerich, et al. (1990) reported an association between lung cancer as an adult and ETS exposure during childhood. They also state, however, that other studies which have investigated such a possible association have failed to confirm the Janerich et al. finding. They then state:

> In the light of the inconsistent findings of other studies, our results on childhood ETS exposure can be plausibly interpreted as sampling fluctuation around a relative risk of 1 (no effect) and do not allow us to conclude that ETS exposure during childhood is protective against lung cancer.

This critique in no way claims that the IARC results on childhood exposure should be interpreted as strong support for a protective effect of ETS exposure on lung cancer. On the other hand, it is interesting to examine this explanation in the context of other ETS epidemiological data. A total of 22 epidemiological studies have been published to date on ETS exposure in childhood. Only one of these studies gave an adjusted RR that was statistically significant, and 12 of these studies gave relative risks less than 1. These results would not appear to be "inconsistent." As a matter of fact the results would appear to have greater consistency than was reported among the IARC study centers for adult (spousal and workplace) exposure. Why then would it be any less correct for the authors to state that in the light of inconsistent findings among the IARC study centers, their results on workplace and spousal ETS exposure can be plausibly interpreted as sampling fluctuation around a relative risk of 1 (no effect) and do not allow them to conclude that ETS exposure is positively associated with lung cancer?

The discussion of the results reported for workplace ETS exposure also warrant examination. The authors state that, "[o]ur results on the effect of ETS exposure at the workplace parallel those of a large US study [Fontham, et al., 1994] in showing a risk similar to that of spousal exposure to ETS and a dose-response relationship." This claim needs to be examined quite carefully. Fontham et al., reported an adjusted OR for reported spousal exposure of 1.23 (95% CI, 0.95-1.57) and an adjusted OR for reported workplace exposure of 1.39 (95% CI, 1.11-1.74). These OR's are indeed of the same magnitude, with the workplace exposure OR being statistically significant. However, it is necessary to note that the unadjusted values were 1.17 (95% CI, 0.95-1.47) and 1.12 (95% CI, 0.91-1.36), respectively. For both OR's adjustment for confounding factors (age; race; study area; education; fruits, vegetables, and supplemental vitamin index; dietary cholesterol; family history of lung cancer; and employment in-high risk occupations) increased the OR's, and the increase for workplace exposure was 225% in terms of excess risk. The IARC study also reports an upward adjustment for the OR for reported workplace exposure, with the unadjusted OR of 1.09 (calculated from the IARC data) increasing to 1.17 (95% CI, 0.94-1.45) when adjusted for age and study center. This upward adjustment of increased risk of 88% for age is not at all surprising. However, IARC reported no further change in the OR when other potential confounders were incorporated into the multiple logistic regression, as might indeed be expected. Therefore, on the basis of this striking difference among the data regarding effect of confounders, it would appear that it is not appropriate to label the results as being similar.

Lastly, in comparing the overall results with the published literature, the authors state, "[w]hen taken together, our results on exposure to ETS during adulthood are in agreement with the available evidence from the United States [Fontham, et al, 1994, Cardenas, et all, 1997]. We think that minor discrepancies between the two studies, such as a somewhat stronger effect of spousal smoking in the U.S. studies and the lack of an effect of 'social' sources in our

study, reflect differences in smoking patterns between the European and U.S. populations." There is no question that the overall results reported in this publication are in line with summary results of already published studies. However, as has been pointed out, this agreement can be assumed to be either the result of a true, albeit extremely weak, association or uncorrected systematic biases. However, once again the authors have appeared to go too far in justifying relatively small differences among studies. The authors have no literature reference to suggest that differences in smoking patterns in Europe and in the US could account for the observed differences in epidemiological results. Experience in both locations would suggest that the opposite is true; that is, that exposure to ETS is more common in Europe than in the US. That is certainly true in the recent past, and if the authors are to be consistent, exposure in the recent past is more important than exposure in the distant past.

E. Conclusions

In one of the largest studies designed to investigate the possible association of ETS exposure with lung cancer, IARC has failed to report a statistically significant relationship for reported exposure by spouse, workplace exposure, exposure in vehicles, and exposure in social situations. IARC claims that despite the lack of statistical significance, their results are in line with other studies on reported ETS exposure and lung cancer. However, as the above analysis demonstrates, the authors have repeatedly investigated possible adjustments to their reported OR's, and in every case they have rejected them as being minor. When a number of "minor" adjustments are made to an extremely weak OR, they accumulate, resulting in a major adjustment. Application of data taken directly from the IARC study publication demonstrate that limited adjustments to the OR's can be made which result in an OR for spousal exposure of 1.08, for workplace exposure of 1.04, and for combined spousal or workplace exposure of 1.04.

This critique does not claim that the adjustments referred to above are exact, since they may not all be necessarily additive, and there is also considerable uncertainty in the adjustments. However, this analysis does show that even limited adjustments to account for multiple systematic errors clearly decrease the OR toward the null value (i.e. no association). This critique agrees with the IARC's overall conclusion that their results are in agreement with other studies on the association of reported ETS exposure and lung cancer. However, the vast majority of such studies failed to investigate the possibility that systematic errors might have biased the results away from the null hypothesis. The authors of this study are to be congratulated for carrying out a detailed analysis of possible biases which could have affected their results, but one must question their decision to dismiss each such bias as being "minor" or their confidence in such weak, variable, results as being demonstrative of an excess risk for lung cancer being associated with reported ETS exposure. The IARC study results, as well as those from other studies, do not convincingly support the opinion expressed in an accompanying commentary on the paper, namely "the inescapable scientific conclusion that ETS is a low-level lung carcinogen" (Blot and McLaughlin, 1998) in humans.

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WSA

IARC Multicenter Case-Control Study of ETS and Lung Cancer:

An Analysis

Study characteristics

WSA

- 12 centers; 7 European countries
- 650 cases; 1542 controls
- Enrollment between 1988 and 1994
- Common questionnaire (excepting translation differences)
  - **Estimates of ETS exposure**
  - **Occupational exposures**
  - **Urban/rural living**
  - **Education* and diet***
- Inter-center and intra-country differences
  - **Response rate**
  - **Selection of controls**
  - **Diagnostic criteria**

*Data on education and diet not available for all centers.

Results

WSA

Reported source of ETS exposure:	OR (95% CI)	Inter-center range	Intra-country (G1/G2/G3) (I1/I2/I3)
Childhood	**0.78*** (0.64-0.96)	0.45 - 2.09	**(0.60/0.82/0.55) (0.62/2.09/0.60)**
Spousal	**1.16 (ns)** (0.93-1.44)	(<0.7 - >1.5)	--
Workplace	**1.17 (ns)** (0.94-1.51)	(8 centers >1.0)	--
Workplace or spousal	**1.14 (ns)** (0.88-1.47)	0.72 - 2.29	**(0.88/1.22/2.01) (0.73/1.12/1.39)**
Overall vehicles	**1.14 (ns)** (0.88-1.48)	0 - 2.85	--
Overall public places	**1.03 (ns)** (0.82-1.29)	0.24 - 2.32	--

*** = Statistically significant. ns = not statistically significant**
G1/G2/G3 and I1/I2/I3 = ORs for German centers 1, 2, and 3 and Italian centers 1, 2 and 3

Estimated effects of some sources of bias

WSA

Source of Potential Bias	Reported Spousal	Reported Workplace	Reported Spousal or Workplace
Unadjusted OR	**1.16**	**1.17**	**1.14**
Misclassification bias	-0.03	-0.03	-0.03
Histological confirmation	-0.03	-0.03	-0.03
Unconditional analysis	-0.01	-0.07	-0.03
Confounding	-0.01	-	-0.01
Estimated overall adjusted OR	**1.08**	**1.04**	**1.04**
Reduction in excess risk	***50%***	***76%***	***71%***

SUMMARY

WSA

- Large, well-conducted study

- No statistically significant overall increased risk reported for any sources of reported ETS exposure
- IARC collected data on many sources of bias, but did not report an OR adjusted for all these factors
- Data presented within the paper indicate that if all the adjustments had been made, the reported excess risk would have been reduced by at least 50%